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June 5, 2000

Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Docket No. 00N-1266 – Comments for Report to Congress on
Pediatric Exclusivity

Dear Sir or Madam:

Agvar Chemicals Inc. (Agvar) is an exclusive distributor of bulk pharmaceutical ingredients made by several major foreign manufacturers of bulk and finished dosage form drugs. Agvar submits the following comments pursuant to the Food and Drug Administration's (FDA's) notice and request for comments on pediatric exclusivity published in the Federal Register of May 5, 2000, 65 Fed. Reg. 26217 (Docket No. 00N-1266). For the reasons stated herein, Agvar requests that the FDA recommend in its report to Congress that pediatric exclusivity not be reauthorized when it sunsets on January 1, 2002. Instead, Agvar requests that the FDA advise Congress either that no incentive is necessary to encourage the development of pediatric drug use data, or, if an incentive is considered necessary, that legislation should be enacted providing for a tax credit for pharmaceutical manufacturers that conduct pediatric drug studies.

Pediatric exclusivity contributes to artificially high prices for sole-source drugs. The resulting inflated health care costs are passed on to patients both directly and indirectly. This negative effect on patients can be largely avoided by a tax credit. A tax credit would also avoid the negative collateral effects on the generic drug industry that result from the unpredictability of the pediatric exclusivity procedure, at least in its current form.

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I. Background

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (FDAMA).¹ Section 111 of FDAMA, "Pediatric Studies of Drugs," amended the Federal Food, Drug, and Cosmetic Act (FDC Act) to add § 505A. This new provision of the FDC Act allows the sponsor of a pending or approved new drug application (NDA) to earn six months of market exclusivity for performing certain studies in pediatric populations.² Pediatric exclusivity extends other types of market protection the NDA sponsor holds under the FDC Act. FDAMA section 111 followed several unsuccessful attempts by Congress to provide an incentive for pharmaceutical manufacturers to develop pediatric data on their drugs.³

Under FDAMA section 111, sponsors can earn six months of additional market protection for NDAs with existing market protection under either the Drug Price Competition and Patent Term Restoration Act⁴ or the Orphan Drug Amendments.⁵ Pediatric exclusivity attaches to an active moiety and not to a specific drug product.⁶ After determining that information about a drug may produce health benefits in a pediatric population, the FDA makes a written request to the NDA sponsor for pediatric studies. A written request may address, among other things, the type of studies to be performed, study design, appropriate study age groups, and clinical endpoints. The FDA may issue a written request at the request of an interested person (i.e., through a proposed pediatric study request (PPSR) from an NDA sponsor) or on its own initiative. The FDA will take approximately 120 days after the agency receives a PPSR to issue a response, in the form of either a written request or a denial of a request. The NDA sponsor is under no obligation to conduct pediatric studies. Reports of studies conducted in response to a written request must meet the terms of the request to qualify for pediatric exclusivity. The studies do not have to result in new labeling or show safety and effectiveness in pediatric patients.

¹ Pub. L. No. 105-115, 111 Stat. 2296 (1997).

² In certain circumstances, the FDA has interpreted FDAMA section 111 to allow a second six-month exclusivity period.

³ See S. 2010, 103d Cong., 2d Sess. (1994); H.R. 4427, 103d Cong., 2d Sess. (1994); S. 1477, 104th Cong., 1st Sess. (1995); S. 2178, 104th Cong., 2d Sess. (1996); H.R. 4277, 104th Cong., 2d Sess. (1996); S. 713, 105th Cong., 1st Sess. (1997); H.R. 1727, 105th Cong., 1st Sess. (1997).

⁴ Pub. L. 98-417, 98 Stat. 1585 (1984) (codified in sections of 15 U.S.C. §§ 68b-68c, 70b (1994), 21 U.S.C. §§ 301, 355, 360cc (1994), 28 U.S.C. § 2201 (1994), and 35 U.S.C. §§ 156, 271, 282 (1994)).

⁵ Pub. L. 97-414, 96 Stat. 2049-56 (1982) (codified as amended at 21 U.S.C. §§ 360aa-360ee (1994)).

⁶ See National Pharm. Alliance v. Henney, 47 F. Supp. 2d 37 (D.D.C. 1999).

FDAMA section 111 directs the FDA to develop, publish, and annually update a list of drugs for which additional pediatric information may improve children's health. The "List of Approved Drugs for which Additional Pediatric Information may Produce Health Benefits in the Pediatric Population" (FDAMA List) was published on May 19, 1998, and revised on May 20, 1999, and May 19, 2000.⁷ A drug is included in the FDAMA List if FDA concludes that it is used in the pediatric population, but insufficient pediatric information appears in the drug's labeling. A drug does not have to be on the list in order for the FDA to issue a written request.

FDAMA section 111 is scheduled to sunset on January 1, 2002.

II. The Effects of Offering Pediatric Exclusivity

Since the initiation of the pediatric exclusivity program, pediatric exclusivity has been granted to 20 drugs. However, FDAMA section 111 has had significant negative effects on both patients, in the form of higher drug prices, and on the generic drug industry, in the form of disruptions in the ability of generic drug companies to make development and production decisions.

Since FDAMA section 111, the FDA has issued regulations authorizing the agency to require NDA sponsors to conduct pediatric studies.⁸ Therefore, it is unnecessary to provide a statutory incentive to conduct such studies. If an incentive is necessary, however, it should not consist of a mechanism that unjustifiably burdens both patients and generic drug companies. Therefore, the FDA should recommend to Congress that FDAMA section 111 not be reauthorized. If there is to be an incentive program to replace pediatric exclusivity, it should be in the form of a tax credit similar to the tax credit currently offered to sponsors of orphan drugs. Especially given the pediatric studies rule, a tax credit should be adequate to bring about the desired level of research into drug use in pediatric populations.

A. Results of the Pediatric Exclusivity Program

Since the passage of FDAMA in November 1997, the FDA has issued written requests for 134 of the drugs from the approximately 450 drugs on the FDAMA List, and has granted exclusivity to twenty of those drugs.⁹ The FDAMA List focuses on

⁷ See Food and Drug Administration, Update of List of Approved Drugs for which Additional Pediatric Information may Produce Health Benefits in the Pediatric Population (last modified Aug. 22, 1999) <<http://www.fda.gov/cder/pediatric/peddrugsfinal.htm>>.

⁸ See 63 Fed. Reg. 66632, 66633 (Dec. 2, 1998).

⁹ See Approved Active Moieties to which FDA has granted exclusivity for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act (last modified May 25, 2000) <<http://www.fda.gov/cder/pediatric/exgrant.htm>>.

cardio-renal and neuropharmacological drugs, which account for nearly one-third of the written requests issued thus far, and which are in the therapeutic areas most often identified with adverse consequences for pediatric patients because of a lack of pediatric data. The number of PPSRs submitted by NDA sponsors varies widely by therapeutic area, but has focused largely on products where patent expiration is imminent or on products for which there is significant sales potential.¹⁰

B. The Negative Effects of Pediatric Exclusivity on Patients and the Generic Drug Industry Can Be Avoided by a Tax Credit

The incentive of pediatric exclusivity is the functional equivalent of inefficient and excessive taxation. For an additional six months, the public is indirectly "taxed" with higher sole-source drug prices. It would be preferable to have a direct tax, such as a tax credit for NDA sponsors. A tax credit would result in higher overall taxes. However, unlike the higher costs produced by pediatric exclusivity, a tax credit would be self-calibrating so as to be proportional to the NDA sponsor's investment in the pediatric studies it conducts.

Some NDA sponsors may conduct expensive clinical investigations to gain pediatric exclusivity; other NDA sponsors may make only a minimal investment to develop data on pediatric uses. Rewarding NDA sponsors in the latter situation with six months of extended FDC Act market protection not only overcompensates them, it results in a greatly expanded range of artificially higher sole-source drug prices, which must be paid by patients and health care providers. Conversely, an NDA sponsor with no existing FDC Act market protection can receive no pediatric exclusivity, and thus cannot have an incentive to develop pediatric data.

A tax credit would not have these disadvantages. A tax credit would be proportional to an NDA sponsor's investment in obtaining data on pediatric uses. It would cost tax dollars, but the overall cost to patients would be far less than they pay in higher prices for drugs granted six months of pediatric exclusivity. And a tax credit could be taken advantage of by NDA sponsors with no existing FDC Act market protection.

A tax credit would have the additional advantage of avoiding the disruptive effect that six-month pediatric exclusivity has on generic drug manufacturers. NDA sponsors often seek pediatric exclusivity for a drug near the expiration of its patent or other form of FDC Act market exclusivity. Generic drug manufacturers plan production based on the anticipated date of patent or exclusivity expiration for the listed drug. If an NDA

¹⁰ Of the ten drugs with more than \$1 billion in worldwide sales and for which FDA has issued written requests, patent expiration is imminent for six of the products. A grant of pediatric exclusivity could be worth more than \$2 billion in revenue for those six drugs. See Tufts Center for the Study of Drug Development, "Impact Report: Drug Firms Embrace Pediatric Study Program During First 2 Years of FDAMA," at 3 (Apr. 2000).

sponsor's intent to apply for pediatric exclusivity is not made publicly known until shortly before its market protection is scheduled to expire, the generic drug manufacturer's significant investment to prepare the generic version for market is often wasted. A tax credit would avoid this disruption.

C. The FDA Should Recommend that Last-Minute Pediatric Exclusivity Be Eliminated and that the Criteria to Qualify for Pediatric Exclusivity Be More Demanding

Even if the FDA does not recommend to Congress that pediatric exclusivity be replaced by a tax credit, the agency should recommend that Congress consider specific changes to the pediatric exclusivity program, including (1) a requirement that pediatric studies be submitted at least two years before the expiration of the last blocking FDC Act market protection, and (2) raising the threshold for drugs to qualify for pediatric exclusivity.

1. Two-year deadline

Generic drug companies make product development plans and manufacturing decisions years in advance of market introduction. In turn, market introduction is determined by the FDC Act marketing protection for the listed drug. That protection is subject to six-month pediatric extension, which can be granted as late as 90 days after the existing FDC Act market protection has expired. Generic drug companies could take pediatric extensions of FDC Act market protection into account if they had timely knowledge that such extensions were a possibility. However, in its current form, the pediatric exclusivity program allows NDA sponsors up until the last day of qualifying for exclusivity to even submit the studies they rely on.¹¹ These last-minute surprises make it difficult for generic drug companies to predict when they will be able to launch their products.

If pediatric exclusivity is reauthorized, the statute should provide that an NDA sponsor must submit pediatric studies no later than two years before the expiration of the last blocking FDC Act marketing protection, and that the FDA must then decide within 90 days whether pediatric exclusivity has been earned. This requirement will allow the FDA to make a decision far enough in advance of the date of earliest generic drug market introduction to permit generic drug companies to make necessary business plans and avoid premature manufacturing of expiration-dated product.

¹¹ One NDA sponsor was recently granted pediatric exclusivity on May 22, 2000, for a drug whose patent was scheduled to expire the same day. The sponsor had submitted the studies themselves one week before that date.

2. Raise the threshold for drugs to qualify for pediatric exclusivity

The FDA is not selective enough in choosing drugs with respect to which pediatric studies will be accepted. The FDA should focus on granting exclusivity to drugs associated with adverse consequences for pediatric patients. The FDA should also more clearly state the types of studies a drug sponsor is required to conduct to earn pediatric exclusivity. Currently, a clinical investigation conducted in response to a written request from FDA may simply include data from pharmacokinetic studies performed by the drug sponsor or from reports of studies conducted by someone other than the NDA sponsor. In exchange for the significant benefit of extended FDC Act market protection, FDA should require drug sponsors to conduct more rigorous studies that justify an addition of relevant pediatric use information to the approved labeling.

D. Pediatric Study Incentives Can Be Eliminated

On December 2, 1998, the FDA issued a rule titled "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients." The purpose of this rule is to ensure the safety and effectiveness of drugs for pediatric patients by requiring NDA sponsors to conduct pediatric studies and include the results of those studies in product labeling.¹²

The pediatric studies rule results in a more targeted identification of gaps in pediatric data than the pediatric exclusivity program under FDAMA section 111. The resources of NDA sponsors can therefore be focused on research and testing for which there is a real need, rather than being used to fund projects whose purpose is in part to defer competition and which may offer little or nothing in the way of potentially useful information on the pediatric use of drugs.

An additional reason to eliminate the pediatric exclusivity program is that its continuation serves as a precedent for additional exclusivity programs for data relating to specific subpopulations of patients or other conditions of use. Such a program has been suggested, for example, for data on drug use in geriatric populations. The trend toward using FDC Act exclusivity to encourage NDA sponsors to conduct additional drug research is pernicious. Brand-name drug companies should conduct necessary drug studies as part of their general obligation to show that their products are safe and effective. For Congress and the FDA to hold out the prospect that particular investigations may result in additional FDC Act marketing protection will have the paradoxical effect of discouraging the conduct of those investigations until such time as Congress authorizes the FDA to grant a reward for them.

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Moreover, the availability, or potential availability, of such marketing protection also encourages brand-name drug companies to engage in segmented research strategies designed not to benefit patients but to maximize marketing protection. Discontinuation of pediatric exclusivity will signal Congress's conclusion that the American public should not have to pay exorbitant amounts of money for each piecemeal increment in knowledge about the safety and effectiveness of drugs. Such a judgment is clearly appropriate. The brand-name drug industry has ample market protection incentives as it is. It does not need more. Drug prices are already high. They do not need to be higher.


Accordingly, the FDA should advise Congress that FDAMA section 111 is no longer necessary and should not be reauthorized.

III. Conclusion

Agvar supports the development of more knowledge about the use of drugs in children. The FDA's 1998 pediatric studies rule provides a means for obtaining such knowledge. Therefore, the FDA should recommend discontinuation of the pediatric exclusivity program. Assuming an incentive program is justified, the pediatric exclusivity program in its current form, and as currently implemented, has negative economic effects on patients and on the generic drug industry. These negative effects can be avoided while still providing an incentive for NDA sponsors to conduct pediatric studies. A tax credit program adequate to provide a meaningful incentive can be designed. FDA should therefore recommend to Congress that, if Congress believes that there needs to be an incentive to develop pediatric data, it should enact a tax credit program. A tax credit would provide a reward proportional to an NDA sponsor's investment in obtaining data on pediatric uses. It would cost far less than extended market protection, thereby eliminating one source of artificially high drug prices. And a tax credit would avoid the disruptive effect that the current pediatric exclusivity program has on the generic drug industry's ability to make informed business decisions. If pediatric exclusivity is retained as part of the FDC Act, the program should be changed to require submission of studies at least two years before expiration of FDC Act market protection and to require the FDA to establish more demanding standards for an NDA drug to qualify for pediatric exclusivity.

Cordially yours,

Agvar Chemicals Inc.


Agnes Varis
President

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